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# Cyclin beyond the Cell Cycle: New Partners at the Synapse

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**In this issue of Developmental Cell, Odajima, Wills, and colleagues (2011) demonstrate that the cell-cycle regulator, cyclin E, sequesters Cdk5, a key regulator of neuronal development and synaptic plasticity. This cell-cycle-independent function of cyclin E reveals an exciting mode of Cdk5 regulation in postmitotic neurons and offers a window into evolutionary parsimony.**

E-type cyclins are members of the core cell-cycle machinery and are required for initiation of DNA replication and S phase progression. Canonical cyclin E signaling regulates the G1 to S phase transit through binding and activation of Cdk2. The expression of cyclin E is tightly regulated at transcriptional and posttranscriptional levels, resulting in phase-specific oscillations during cell-cycle progression. While transcriptional control is primarily exerted via the activity of the transcription factor E2F, proteosomal degradation is largely responsible for rapid degradation of cyclin E protein.

In a tour de force study, reported in this issue of *Developmental Cell*, Odajima, Wills, and other colleagues from the laboratories of Jarrod Marto and Piotr Sicinski now demonstrate that cyclin E regulates synapse formation by sequestering Cdk5 in postmitotic neurons (Odajima et al., 2011). Building on previous observations of elevated cytoplasmic cyclin E levels in terminally differentiated neurons (Ikeda et al., 2011; Miyajima et al., 1995), these authors demonstrate that Cdk5 forms a catalytically inactive complex with cyclin E promoting synapse formation. Deletion of cyclin E resulted in a lesser number of synapses and impaired synaptic transmission in cultured hippocampal neurons. Similarly, acute cyclin E shutdown caused a reduction of dendritic spines in CA1 hippocampal neurons. In complementary experiments, overexpression of Cdk5 phenocopied cyclin E deletion while loss of Cdk5 activity in cyclin E-deficient neurons rescued the synaptic phenotypes.

Interestingly, no developmental defects were observed when both E-type cyclins were ablated in neurons early in development. This suggests a specific role for cyclin E in postmitotic neurons, but it appears to be dispensable for proliferation of neuronal progenitors. Biochemical analysis of cyclin E-ablated brains revealed heightened phosphorylation of Cdk5 substrates at Cdk5 sites; consistent with the cyclin E-mediated inhibitory sequestration of Cdk5. In line with previous work showing Cdk5 impaired NMDA receptor assembly (Chergui et al., 2004), cyclin E null brains showed reduced surface expression of the NR1 NMDA receptor subunit. In accordance with this observation, electrophysiology revealed reduced sEPSC frequency in the CA1 pyramidal neurons of the cyclin E knockout brains, including a significant reduction in the NMDA component.

Finally, the authors tested synaptic plasticity and memory directly, focusing their attention on NMDA receptor-dependent properties of the CA1 neurons. Theta-burst-induced LTP in CA1 neurons was reduced in cyclin E null brains. In vivo tests revealed impaired spatial learning and memory and cognitive flexibility in these mice. Significantly, Cdk5 conditional knockout mice have been shown to have the opposite effects: reduced induction threshold for LTP, improved spatial memory, and enhanced reversal learning (Hawasli et al., 2007).

Odajima, Wills, and colleagues (2011), in an elegant series of experiments spanning quantitative proteomics to behavioral tests, have thus demonstrated a novel function of cytoplasmic cyclin E in restraining the activity of Cdk5 and influencing synaptic plasticity. This demonstration of a cell-cycle regulator being employed as a critical mediator of synaptic function may be a result of evolutionary parsimony, and neurons appear to have picked up this strategy as a general mechanism. Recently, several proteins involved in cell-cycle regulation and maintenance of genomic stability have been shown to regulate postmitotic neuronal physiology. This list includes the Anaphase-Promoting Complex, Ataxia Telangiectasia Mutated, Polo-like kinases, Origin Recognition Complex, and Aurora kinase (Frank and Tsai, 2009). It remains to be seen if a terminal differentiation-triggered switch is in operation. Similarly, the uniqueness of neurons among other postmitotic cells remains unclear; unlike in neurons, cyclin E expression is shut down in postmitotic muscle cells. Colocalization analysis by Odajima, Wills, and colleagues (2011) shows that there are neuronal populations without cyclin E expression. Thus, a system maintaining high cyclin E levels may be present in a subset of neurons, making this regulatory step more intriguing. Ubiquitin-proteosomal degradation is a major regulator of cyclin E levels; it will be important to see whether this system is affected when cyclin E is in a complex with Cdk5.

While reduction of dendritic spines and its functional consequences in cyclin E-knockout brains are convincingly demonstrated, the mechanistic details of this process are likely to be of importance. Cdk5 is phosphorylated by activated EphA4 and can mediate spine retraction via activating RhoA via the RhoGEF ephexin (Fu et al., 2007). It is possible that the cyclin E-mediated sequestering may prevent similar activation of Cdk5 and contribute to spine maintenance.

Synaptic plasticity and processes involved in learning and memory have critical temporal components. It is therefore essential to investigate whether the rate-limiting action of cyclin E on Cdk5 activity

is dynamically modulated. If Cdk5 activity is critical for synaptic plasticity, one expects changes during the process of learning and cyclin E-Cdk5 interactions may represent such a regulatory node.

Returning to the cell cycle, Cdk5 may function as a cell-cycle suppressor in postmitotic neurons and drive differentiation (Zhang et al., 2008). It is therefore of importance to track, through development, the association of cyclin E with Cdk5. While Odajima, Wills, and colleagues (2011) have attempted this in their proteomic analysis, greater spatiotemporal resolution would be necessary to address this question. Stress conditions, including pathological stresses, are known to drive neurons into the cell cycle and subsequent neuronal death. It is possible that cell-cycle re-entry may involve modulation of the interaction between cyclin E and Cdk5.

It appears that a group of core cell-cycle regulators, cyclin E being the latest to be identified, have evolved to function in a considerably different cellular milieu. Sequestration of Prospero in *Drosophila* (Berger et al., 2010) and atypical Cdks, such as Cdk5 (as shown here), are interesting examples involving cell-cycle-independent functions of cyclin E. Thus, cyclins appear to have extended their posttranslational regulatory functions beyond the cell-cycle. Future work should provide interesting insights into evolutionary logic of these "dual specificity" proteins, but it appears proliferation and differentiation may form a continuum with the same players employed parsimoniously in multiple contexts.

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# The Hormone of Love Attracts a Partner for Life

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**Neurovascular integration during embryonic development is essential for adult physiology. In this issue of *Developmental Cell*, Gutnick et al. (2011) report that hypothalamic neurons secrete oxytocin as a guidance cue for endothelial cells to establish their vascular supply—a prerequisite for neuroendocrine secretion from the neurohyophysis in adult life.**

The nervous and vascular systems are functionally different but form networks that are often in close association and communication. This is exemplified by the vascularization of axon bundles or, conversely, by the innervation of muscular vessels with the autonomic nerves that control vascular tone. Much research effort has been directed at identifying the molecules that guide these interactions (reviewed by Segura et al., 2009). For example, it has been shown that nerve-cell-derived VEGF promotes the arterial differentiation of blood vessels that are coaligned with peripheral nerves (Mukouyama et al., 2005) and that endothelial cells of the external carotid artery guide sympathetic axons by releasing chemoattractive endothelins (Makita et al., 2008). In contrast, the molecular and cellular mechanisms that establish the neurovascular interface of neuroendocrine organs such as the posterior pituitary have not been identified. In this issue of *Developmental Cell,* Gil Levkowitz and colleagues demonstrate how hypothalamic axons regulate endothelial morphogenesis to induce the neurovascular congruence that provides the anatomical basis for neuroendocrine secretion from the posterior part of the pituitary (Gutnick et al., 2011) (Figure 1).

Magnocellular neurons in the hypothalamus extend axons to interface with fenestrated capillaries in the posterior pituitary, the neurohypophysis, to release the neuropeptides oxytocin and vasopressin into the bloodstream (reviewed by Burbach et al., 2001). Oxytocin, a word that in Greek means "quick labor," is often referred to as the hormone of love for its multiple roles in sexual